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TOPICAL REVIEW

The pontine REM switch: past and present

Patrick M. Fuller, Clifford B. Saper and Jun Lu

Department of Neurology, Division of Sleep Medicine, and Program in Neuroscience, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

Rapid eye movement (REM) sleep is a behavioural state characterized by activation of the cortical and hippocampal EEG, rapid eye movements and muscle atonia. For the past 30 years, the most widely accepted neural circuitry model for the regulation of REM sleep has emphasized reciprocal inhibitory interactions between pontine brainstem monoaminergic and cholinergic neurons. In general support of the reciprocal interaction model, neuropharmacological studies have shown that cholinergic agonists promote REM sleep and muscarinic antagonists and monoamines inhibit REM sleep. It has nevertheless proven difficult to reconcile both the theoretical framework of this model and the pharmacological data with the fact that selective lesions of either cholinergic or monoaminergic (noradrenergic, serotoninergic or dopaminergic) nuclei in the brainstem have relatively limited effects on REM sleep. Recent work by our laboratory has revealed the presence of non-cholinergic and non-monoaminergic mutually inhibitory REM-off and REM-on areas in the mesopontine tegmentum that may form the neuroanatomical basis of the switching circuitry for REM sleep. These findings posit a REM switching circuitry model that is analogous to an electronic 'flip-flop' switch. In this flip-flop switch arrangement, GABAergic REM-on neurons (located in the sublaterodorsal tegmental nucleus (SLD)) inhibit GABAergic REM-off neurons (located in the ventrolateral periaqueductal grey matter (vlPAG) and lateral pontine tegmentum (LPT)) and *vice versa*. In the REM-on area are two populations of glutamatergic neurons, the first of which projects to the basal forebrain and regulates EEG components of REM sleep and the second of which projects to the ventromedial medulla and spinal cord and regulates atonia during REM sleep. Our findings demonstrating independent pathways mediating atonia and the EEG components of REM provide a basis for their occasional dissociation in pathological states, e.g. REM sleep behaviour disorder.

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Corresponding author J. Lu: Department of Neurology, Division of Sleep Medicine, and Program in Neuroscience, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA. Email: jlu@bidmc.harvard.edu

The behavioural state of rapid eye movement (REM) sleep was first described more than 50 years ago (Aserinsky & Kleitman, 1953; Dement, 1958; Jouvet & Michel, 1959). REM sleep in humans and other mammals is characterized by the appearance of fast, desynchronized rhythms in the cortical EEG, rapid eye movements, autonomic activation and a loss of muscle tone. As the cortical EEG of REM sleep closely resembles that of the waking state, REM sleep has been alternatively termed 'paradoxical sleep' or, by some investigators, 'active sleep'. In 1949, before REM sleep was first described, Moruzzi and Magoun discovered an 'ascending reticular activating system' (ARAS), originating in the mesopontine reticular formation, which controls cortical arousal and awareness (Moruzzi & Magoun, 1949). The ARAS consisted of populations of neurons in the midbrain and pontine reticular formation that were thought to play a critical role in tonic EEG desychronization via thalamic and hypothalamic relays. The striking similarities between the waking and REM EEG suggested early on an important role for the ARAS in producing the desynchronized EEG of REM sleep. While some progress has been made in recent years, major gaps remain in the effort to delineate (1) the locus of the pontine switching circuitry for REM sleep, (2) the neurotransmitters regulating REM phenomenon, i.e. muscle atonia, activation of the cortical and hippocampal EEG, and (3) how dysfunction of this circuitry may form the neuropathological basis of REM sleep behaviour disorder.

In one of the first published studies on REM sleep mechanisms, Jouvet & Michel, 1960) demonstrated that physiological REM sleep was blocked by systemic

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administration of atropine sulphate and enhanced by physostigmine, suggesting that the neurotransmitter acetylcholine promoted REM sleep. Two years later, Jouvet (1962) demonstrated that electrical stimulation of the caudal mesencephalic region or pontine tegmentum produced a desynchronized sleep-like state in cats that was, except in duration, indistinguishable from physiological REM sleep. Transections at this level (i.e. the 'pretrigeminal' cat preparation) had previously been shown to result in chronic EEG desynchronization (Batini *et al.* 1958). Studies in the 1970s and 1980s revealed that the ARAS (i.e. the cortical 'desynchronizing' system) originated in a series of cell groups with different neurotransmitters that, in general, demonstrated profound state-dependent activation (for review see Jones, 2003; Saper *et al.* 2005; Fuller *et al.* 2006). The juxtaposition of these independent experimental observations led to the long-standing hypothesis that mesopontine cholinergic nuclei are responsible for the tonic activation of thalamocortical systems associated with the desynchronized EEG of waking and REM sleep. Neuropharmacological experiments over the next two decades provided support for the 'mesopontine cholinergic' hypothesis. For example, microinjections of cholinergic agonists or the anti-cholinesterase antagonist neostigmine (which blocks the breakdown of synaptic acetylcholine) into the pontine reticular formation, but not the midbrain or medullary reticular formation, produced a dose-dependent enhancement of REM sleep (Amatruda *et al.* 1975; Baghdoyan *et al.* 1984; Vanni-Mercier *et al.* 1989; Yamamoto *et al.* 1990).

To a great extent, the early studies by Jouvet and others guided the development of McCarley & Hobson's (1975) theoretical 'reciprocal interaction' model of the switching circuitry regulating REM sleep generation. This model, which until recently remained the most widely accepted model of the REM sleep regulation, cast the pontine REM switching circuitry as a population of presumptive cholinergic neurons of the mesopontine tegmentum (which fire most rapidly during REM sleep, hence 'REM-on' neurons) and brainstem monoaminergic neurons (which cease firing during REM sleep, hence 'REM-off' neurons) that reciprocally interact to generate the ultradian rhythm of REM sleep. In the original model, REM-on cholinergic neurons of the medial pontine reticular formation (mPRF) are essential for the generation of the tonic and phasic physiological events of REM sleep, e.g. neocortical EEG activation, atonia and ponto-geniculo-occipital (PGO) waves (for review see Kubin, 2001; McCarley, 2004). During waking, the cholinergic REM sleep generator is tonically inhibited by REM-off monoaminergic neurons, but during non-REM sleep (NREM) sleep inhibitory monoaminergic tone gradually wanes and cholinergic excitation waxes until eventually REM sleep is generated. This model has been modified several times over the past 30 years, although the basic framework, i.e. aminergic–cholinergic interplay, has remained the same (for review see Pace-Schott & Hobson, 2002). For example, it was determined that the major locus of the mesopontine cholinergic neurons was not the mPRF but rather the peribrachial cell groups (i.e. near the superior cerebellar peduncle, also known as the brachium conjunctivum), the pedunculopontine and laterodorsal tegmental nuclei (PPT–LDT). Cholinergic PPT–LDT neurons give rise to ascending projections to the thalamus, are most active during waking and REM sleep and are considered the major source of upper brainstem input to the thalamic relay and reticular nuclei (Krout *et al.* 2002). In general, neuropharmacological and electrophysiological experiments have provided strong support for the pontine reciprocal interaction model and the critical role for the PPT–LDT neurons as REM-on cell groups. Nevertheless, the accuracy of the reciprocal inhibition model has been contested by several experimental findings including: (1) limited alterations in REM sleep following selective lesions of brainstem cholinergic and monoaminergic nuclei (Jones *et al.* 1977; Mouret & Coindet, 1980; Shouse & Siegel, 1992; Lu *et al.* 2006) and (2) limited c-Fos expression in *cholinergic* LDT and PPT neurons during REM sleep (Verret *et al.* 2005; Lu *et al.* 2006). It should be noted that Webster & Jones (1988) reported that lesions of the LDT and PPT reduced the amount of time spent in REM sleep in cats; however, close inspection of the histology revealed that the lesions included the peri-locus coeruleus alpha (the SLD in rats), a region containing putative REM-on neurons (see below). Thus, to reconcile the apparent incongruities between the widely accepted cholinergic–aminergic model and experimental work, our laboratory recently performed a series of studies to delineate the pontine switching circuitry for REM sleep.

To identify the brainstem circuitry for generating REM sleep (atonia, activation of the hippocampal and cortical EEG, and rapid eye movements), we traced the convergence of two descending pathways from hypothalamic nuclei previously established to be involved in the control of REM sleep in rats: the extended ventrolateral preoptic nucleus (eVLPO), which contains REM-active neurons (Lu *et al.* 2002) that are inhibitory but promote REM sleep, and orexinergic neurons of the lateral hypothalamus (LH), which cease firing during REM sleep (Kiyashchenko *et al.* 2002; Lu *et al.* 2002; Lee *et al.* 2005), but are excitatory and presumably inhibit REM sleep. These observations would predict that these projections would act on a target that consisted of REM-inhibitory neurons. Following a tracer injection into the VLPO and immunohistochemical staining of orexin terminals, we observed several areas of convergence in the mesopontine tegmentum, including: the ventrolateral periaqueductal grey (vlPAG) and lateral pontine tegmentum (LPT), dopaminergic neurons of the ventral PAG, dorsal raphe nucleus (DRN) and the locus coeruleus. The vlPAG and LPT (situated between the oral pontine nucleus and PPT in the rat) were particularly attractive candidate regions to contain a REM-off cell population as it has been reported that injections of the GABA agonist muscimol into these regions triggered large amounts of REM sleep in cats (Sastre *et al.* 1996). Moreover, pretreatment with bicuculline blocked the REM-inducing effects of muscimol in guinea pigs (Vanini *et al.* 2007). Consistent with these earlier reports, we found that cell-specific lesions of the vlPAG and LPT doubled REM sleep and increased both the number and duration of bouts of REM sleep (Lu *et al.* 2006). Control lesions of the median or dorsal raphe nucleus, but sparing the vlPAG, or cell-specific lesions of the mPRF, but sparing the LPT, did not produce any significant effects on REM sleep.

Following the identification of this putative REM-off region, we hypothesized that these neurons may prevent REM sleep by inhibiting a population of REM-on cells. To identify possible candidates, we anterogradely traced projections of the vlPAG–LPT in animals in which Fos-active neurons had been stained during a period enriched for REM sleep. This approach identified a putative REM-on region which included the sublaterodorsal nucleus (SLD) (equivalent to the subcoeruleus (SC) or peri-locus coeruleus alpha (peri-LCa) of the cat brain) as well as a dorsal extension of the SLD, and the adjacent regions of the precoeruleus area (PC; see REM EEG control below) of the periventricular grey matter and the medial parabrachial nucleus (MPB). Notably, the SLD, which is located ventral to the caudal LDT and Barrington's nucleus and rostral to the LC, had long been viewed as a likely potential site for a 'REM-on' cell population (e.g. Sakai *et al.* 1979; Sakai, 1986). In general support of this concept it has been demonstrated that stimulation of the SLD with bicuculline (GABA antagonist) induced REM sleep in rats and cats (Xi *et al.* 1999; Boissard *et al.* 2002) whereas injection of muscimol (GABA agonist) into this same region decreased REM sleep (Xi *et al.* 1999). In addition, REM-active cells (as identified with Fos and extracellular recordings) have been observed in this region (Sakai, 1986; Verret *et al.* 2005; Lu *et al.* 2006), as opposed to the cholinergic mesopontine neurons, which, despite their putative REM-on activity profile, do not show Fos during REM sleep (Boissard *et al.* 2002; Verret *et al.* 2005; Lu *et al.* 2006). Thus, having identified putative 'REM-on' (i.e. SLD–PC–PB) and 'REM-off' (i.e. vlPAG–LPT) neurons, we next demonstrated that neurons in the SLD and the vlPAG–LPT that target each other contain glutamic acid decarboxylase (GAD67) mRNA (i.e. are GABAergic neurons). This circuit arrangement of mutual inhibitory interactions between the vlPAG–LPT REM-off and SLD REM-on neurons suggested a flip-flop switch arrangement in which each side (by inhibiting the other) also disinhibits (and thus reinforces) its own firing (see below and Fig. 1).

REM atonia control

In the 1960–70s, two groups led by Michel Jouvet in Lyon (Mouret *et al.* 1967) and Adrian Morrison (Henley & Morrison, 1974) in Philadelphia showed that cats with lesions in the subcoeruleus region of the brainstem exhibit a form of dream 'enactment', e.g. head raising, locomotion, attempting to catch mouse, during REM sleep and named this unique behaviour 'oneiric behaviour' (Jouvet) or REM-without-atonia (Morrison). In 1986, Schenck and colleagues (Schenck *et al.* 1986) documented a similar phenomenon in some humans and termed this state 'REM behaviour disorder' (RBD). Progress in studying this phenomenon was initially held back by the observation that lesions of the 'subcoeruleus region' in rats produced only transient REM-without-atonia (Sanford *et al.* 2001). However, recent studies that identified the SLD as a key REM-on site suggest that the cell group that is equivalent to the 'subcoeruleus' region in rats, is probably about 1 mm rostral to the LC and subcoeruleus region, in the SLD. Subsequent cell-specific lesions of the ventral SLD in rats replicated the chronic inability to maintain atonia and animals exhibited simple and complex motor behaviours while in REM sleep, as seen in cats (Lu *et al.* 2006).

We next sought to identify the pathways by which the vSLD might produce muscle atonia by tracing the descending projections of the vSLD. As in earlier reports, we traced axons through the medial pontine and medullary reticular formation to the spinal ventral horn. As it has been long hypothesized that premotor neurons in the gigantocellular reticular nuclei of the ventromedial medulla (Sastre *et al.* 1981; Soja *et al.* 1987; Morales *et al.* 2006) are crucial for REM atonia, we placed large lesions in this site. Consistent with Jouvet's previous study in cats (Sastre *et al.* 1981) in which kainic acid lesions of the gigantocellular, but not magnocellular, tegmental fields of the pontine and rostral medulla failed to alter REM atonia, we found that cell-specific lesions in the rostral ventromedial medulla (RVM) did not affect tonic atonia during REM (Lu *et al.* 2006). This finding, however, is perhaps not surprising considering the paucity of RVM projections to the ventral motor horn (Skagerberg & Bjorklund, 1985). On the other hand, we recently found that cell-specific lesions of the intermediate ventromedial medulla (IVMM, which extends from the beginning of the inferior olive to the beginning of the area postrema) produced myoclonic jerking in rats, suggesting a role for REM-on IVMM neurons in the inhibition of phasic, but not tonic motor activity during the atonia of REM sleep (Lu J & Fuller PM, unpublished observations). This region, which represents anatomically a restricted rostral–caudal segment of the gigantocellular reticular field, had previously been implicated in mediating the atonia of REM sleep (Lai & Siegel, 1988). Thus, available data are consistent with the hypothesis that the medulla contains

REM-on cells that promote, but are not sufficient to produce, atonia during REM sleep.

As our data suggest that the primary tonic control mechanism for producing the atonia of REM sleep does not involve a medullary relay, we injected a retrograde tracer (Flurogold (FG)) into the spinal ventral horn to identify inputs from REM-on neurons. Virtually all FG-labelled SLD neurons contained mRNA for VGLUT2 and none were immunoreactive for choline acetyl-transferase, indicating that the SLD sends primarily glutamatergic projections to the spinal ventral horn. Finally, labelled neurons from our SLD tracer injections formed appositions with parvalbumin-immunoreactive neurons in lamina VIII, most of which belong to the class of V1 interneurons that innervate motor neurons with terminals containing glycine, GABA or both. Thus, in combination with the results from our SLD lesions, our tracer studies suggest that the SLD probably produces the atonia of REM mainly by means of direct glutamatergic inputs to glycinergic/GABAergic interneurons of the spinal ventral horn (Lu *et al.* 2006). We have not yet established whether SLD inputs to the IVMM and spinal cord are independent parallel pathways or if they represent collateral axon projections from the same SLD neurons.

From a clinical perspective, these findings may also provide a framework for understanding the pathophysiology of REM-sleep-related disorders such as RBD. RBD is a parasomnia that typically is manifested as 'dream enactment' behaviour, i.e. involuntary nocturnal movements that include kicking, punching, shouting and screaming during REM sleep (for review see Boeve *et al.* 2007). RBD may represent an early pathophysiological manifestation of evolving Parkinson's disease (PD) and other Lewy body disorders, (LBD) e.g. Lewy body dementia and pure autonomic failure. Indeed, RBD may be manifested as much as a decade prior to the motor and cognitive symptoms of PD and thus the diagnosis of RBD may provide an early therapeutic window for delaying or preventing the full development of PD (Olson *et al.* 2000; Boeve *et al.* 2001; Gagnon *et al.* 2006*a*,*b*). Although the brainstem is clearly implicated in RBD pathogenesis, the identity of the neural networks that become dysfunctional in RBD is currently unknown. Our recent studies suggest the possible critical role for the subcoeruleus or SLD region in RBD pathogenesis. The concept of SC/SLD dysfunction (as the neuropathological substrate for RBD) is seemingly consistent with the temporal pattern of neuronal degeneration in PD and other LBD, which starts in the brainstem and includes the coeruleus–subcoeruleus complex in earlier stage (I–II) of Parkinson's disease, and progresses inexorably rostrally towards the forebrain (Braak *et al.* 2000, 2001, 2005). The temporal pattern of lesions, i.e. caudal-to-rostral progression, is thus also consistent with RBD (secondary to SC/SLD degeneration) as an early manifestation of these neurodegenerative conditions. Nevertheless, although SC/SLD dysfunction has been demonstrated in PD it remains unclear if RBD in evolving PD is caused by SC/SLD degeneration. Interestingly, however, Mathis *et al.* (2007) recently reported a rare case of RBD in a 30-year-old individual with an encephalitis-induced lesion that was restricted to the dorsal pontine tegmentum (presumably involving the subcoeruleus region bilaterally).

REM EEG control

The REM EEG in rodents is characterized by hippocampal theta activity (∼4–7 Hz). Hippocampal theta oscillations are generated by cholinergic and GABAergic inputs from theta pacemaker neurons of the medial septum and vertical limb of the diagonal band, which receive and transform tonic ascending inputs from the brainstem (Kocsis & Kaminski, 2006). To determine the origin of the ascending inputs driving REM hippocampal theta, we injected the retrograde tracer CTB into the medial septum. Following the tracer injection, we found that the retrogradely labelled REM-on cells were mainly concentrated in the precoeruleus (PC) region and were glutamatergic. Cell-specific lesions of the PC abolished theta oscillations during sleep and thus REM sleep was identifiable only by episodic atonia and desynchronized EEG (Lu *et al.* 2006). Our data thus provide support for the concept that glutamatergic inputs from the REM-on PC region to the medial septum drive hippocampal theta during REM sleep.

The REM switch

The original reciprocal inhibition model, which conceptualized the REM switching circuitry as interactions of pontine aminergic and cholinergic neurons, has been accepted for more than a quarter of a century as the basis for understanding the neuronal substrates of REM sleep generation. As detailed above, recent work has revealed the critical role of several non-cholinergic and non-aminergic REM-on and REM-off GABAergic cell populations in the pontine brainstem that form the basis of a flip-flop switch circuit arrangement for REM sleep control. These results also suggest that brainstem aminergic and cholinergic groups are more correctly characterized as REM modulators and not REM generators. For example, cholinergic neurons of the PPT–LDT are REM-on and may inhibit the LPT (as cholinergic agonists injected into this region cause REM states), but are not directly inhibited by the LPT and thus the PPT–LDT is not part of the mutually inhibitory flip-flop switch. Alternatively, REM-on PPT–LDT cholinergic neurons may excite REM-on SLD neurons. Similarly, serotoninergic dorsal raphe (DRN) and noradrenergic locus coeruleus neurons (LC) may inhibit

REM-on SLD neurons or activate REM-off circuitry. Delineating these mechanisms may provide insight into how monoamine inhibitors, such as anti-depressants, can dramatically suppress REM sleep. Nevertheless, like the PPT–LDT, DRN–LC neurons are not inhibited directly by the SLD, and hence are not a part of the mutually inhibitory flip-slop switch.

In summary, recent work by our laboratory has uncovered three REM-on groups with distinct projections and neurotransmitters. The SLD contains glutamatergic neurons that project to the spinal cord and GABAergic neurons that project to REM-off neurons in the vlPAG and LPT. The PC and PB also contain glutamatergic neurons, but these neurons project to the basal forebrain

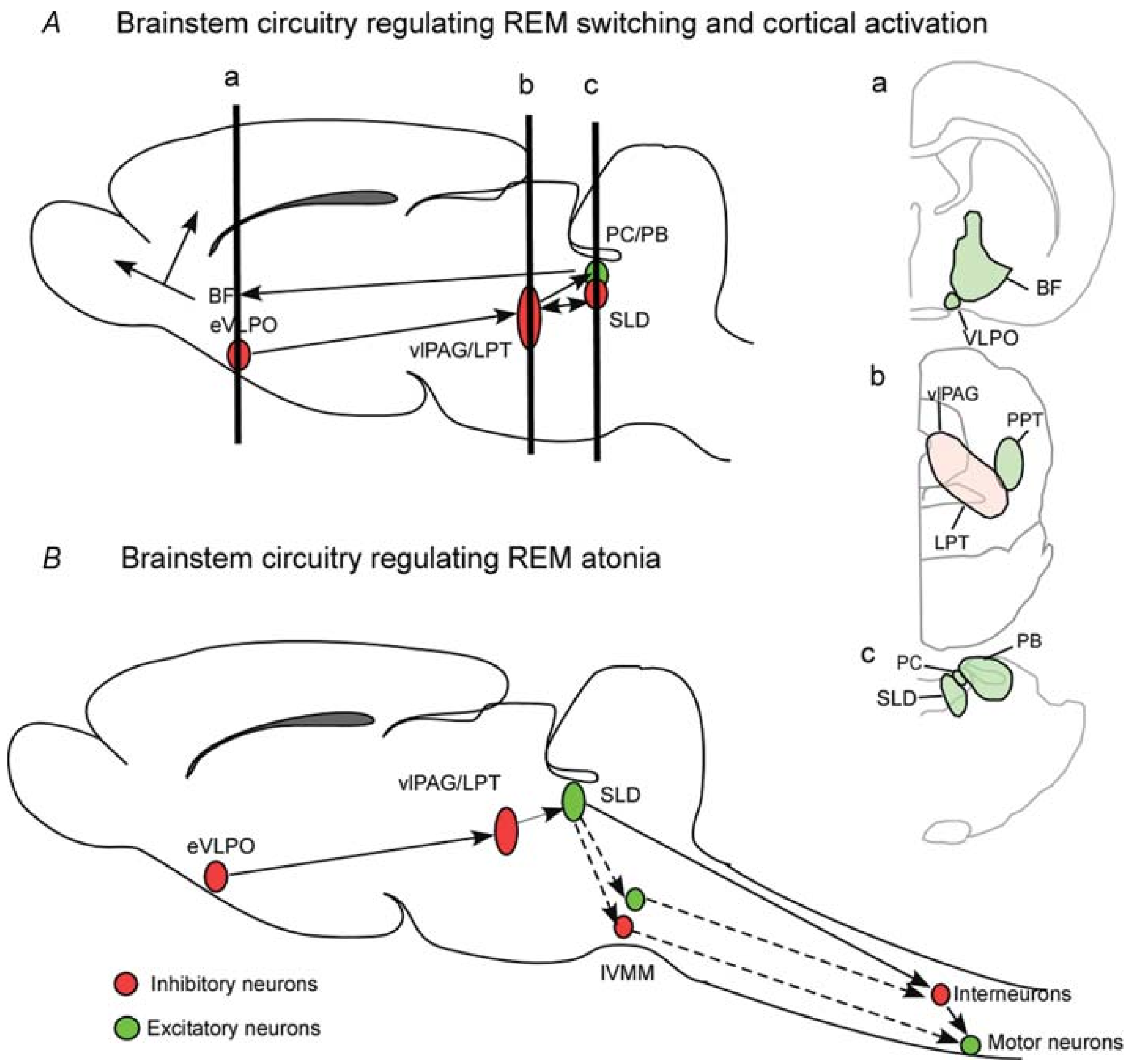

Figure 1. Pontine REM Circuitry
In the REM sleep flip-flop circuit model, the extended VLPO (eVLPO) inhibits REM-off GABAergic neurons in the vlPAG and LPT which, in turn, inhibit three populations of REM-on neurons in the dorsolateral pontine quadrant: (1) glutamatergic neurons in the PC and PB, which project to the medial septum–basal forebrain, and activate the hippocampus and neocortex; (2) GABAergic neurons in the SLD that feedback onto the vlPAG–LPT REM-off neurons; and (3) glutamatergic neurons in the SLD that project to glycinergic/GABAergic interneurons in the spinal ventral horn which, in turn, inhibit motor neurons to produce (tonic) atonia. The SLD glutamatergic neurons also project to a region of the intermediate ventromedial medulla (IVMM) containing neurons that project to spinal ventral horn; however, it is not known if this projection is excitatory or inhibitory nor is it known if these projections are direct (i.e. spinal motor neuron) or indirect (i.e. spinal interneuron). We hypothesize that these IVMM neurons may play a role in suppressing myoclonic jerking (i.e. phasic increases in muscle tone) during REM sleep. Thus, activation of the eVLPO triggers a cascade of changes including activation of the cortical/hippocampal EEG and atonia during REM sleep. Cholinergic and monoaminergic systems may modulate REM sleep via acting on either the REM-off or REM-on groups or on both simultaneously (not shown), although the cholinergic and monoaminergic systems are located external to the REM switch.

and medial septum and regulate REM EEG in the cerebral cortex and hippocampus. Thus, lesions of the SLD, vSLD and PC produce a specific loss of REM sleep components: REM sleep, atonia and theta EEG, respectively. Our model for the regulation of REM sleep therefore predicts a circuit arrangement similar to a ‘flip-flop’ switch wherein REM-off neurons in the vlPAG–LPT inhibit all three REM-on groups and GABAergic REM-on SLD neurons feed back to the REM-off neurons. In contrast to the original reciprocal interaction model which emphasized interactions of cholinergic and monoaminergic neurons, our model hypothesizes that the switching circuitry for REM sleep involves reciprocal interactions between GABAergic REM-off and REM-on populations. The ‘flip-flop’ model for REM sleep maintenance and generation is available for empirical testing and it is our hope that this model will provide a context for understanding the neuropathological basis and aetiology for a variety of sleep disorders. Our laboratory is currently performing studies to evaluate the effects of focal disruption of mesopontine glutamatergic, GABAergic and cholinergic signalling on REM sleep phenomena as well as electrophysiological characterization of how cholinergic and monoaminergic systems influence the REM flip-flop switch.

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